



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

February 28, 2007

**MEMORANDUM**

**SUBJECT:** Coumaphos: Human Health Risk Assessment for Proposed Use on Honey and Honeycomb. PC Code: 036501; Petition Number: 2E6504; DP Number: D315769.

Regulatory Actions:                      Section 3  
Risk Assessment Type:                  Single Chemical/Aggregate

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## 1.0 Executive Summary

### *Background*

Coumaphos (O-[3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl] O,O-diethyl phosphorothioate) is an organophosphate insecticide/acaricide currently used for the control of mites and insects on livestock. Permanent tolerances are established for the residues of coumaphos and its oxygen analog (coumaphos-PO) at 1.0 ppm in fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep, along with a tolerance at 0.5 ppm in milk fat. The Agency has granted Section 18 emergency exemptions for the use of coumaphos on beehives to control varroa mites and/or small hive beetles in 40-46 states, starting in 1999 as a non-food use. In 2000, these Section 18s were reclassified as a food use, and time-limited tolerances were first established for residues of coumaphos and its oxygen analog at 0.1 and 100 ppm, respectively, in honey and honeycomb; these tolerances expire on 12/31/2007.

This assessment addresses the risks associated with making the use of coumaphos on beehives permanent. Interregional Research Project #4 (IR-4) has submitted a petition proposing a Section 3 registration for the use of coumaphos-impregnated strips in beehives for the control of varroa mites and small hive beetles. The strips (CheckMite+ Bee Hive Pest Control Strips) contain 10% coumaphos, the active ingredient (ai), by weight. The proposed label would allow for use of up to two 10% strips hung in the hive's brood chamber for control of varroa mites, and the concurrent use of another 10% strip attached to the bottom board for control of small hive beetles. The strips could remain in the hive for up to 45 days, and the application could be made at anytime during the year, including during honey flow (honey accumulation). In conjunction with this use, the petitioner is proposing permanent tolerances for the combined residues of coumaphos and coumaphos-PO at 0.1 ppm in honey and at 100 ppm in honeycomb (beeswax).

### *Hazard Characterization*

The mammalian toxicology database for coumaphos is complete. Acute toxicity studies in rats and rabbits; an acute delayed neurotoxicity study in hens; subchronic oral and dermal studies in rats; chronic/carcinogenicity studies in rats, mice, and dogs; developmental toxicity studies in rats and rabbits; a two-generation study in rats; mutagenicity studies; and a metabolism study were discussed and considered in the Reregistration Eligibility Decision (RED) for coumaphos (<http://www.epa.gov/oppsrrd1/REDs/0018.pdf>). Acute and subchronic neurotoxicity studies in rats were received subsequent to the RED and were considered in the Reregistration Eligibility Decision Addendum and FQPA Tolerance Reassessment Progress Report (TRED) for coumaphos (<http://www.epa.gov/oppsrrd1/REDs/0018tred.pdf>). Subsequent to the TRED, a developmental neurotoxicity study and a comparative cholinesterase study in rats were received; these studies are discussed and considered in the current risk assessment.

The acute toxicity of coumaphos is high via the oral route of exposure (Category I), moderate via the inhalation route (Category II), and slight via the dermal route (Category III). Coumaphos is not a dermal sensitizer or a dermal irritant, and it does not cause delayed neuropathy. As an organophosphate insecticide, coumaphos primarily affects the nervous system through cholinesterase (ChE) inhibition, although systemic toxicity in the form of decreased body weight gains was observed in chronic studies. Females are consistently more sensitive to the cholinergic

effects than males. In developmental toxicity studies in rats and rabbits, no developmental toxicity was observed, while clinical signs of ChE toxicity were seen in the maternal animals. In a two-generation reproduction study, ChE inhibition was noted in both parents and offspring, with parents more susceptible; reproductive toxicity was not observed. A comparative ChE study demonstrated increased quantitative susceptibility of the offspring in that ChE inhibition was seen at a lower dose in neonatal pups, compared to young adults. Coumaphos is not carcinogenic and is classified as a Group E chemical, indicating that it is "Not Likely" to be carcinogenic in humans via relevant routes of exposure. No evidence of mutagenicity was seen in any study.

#### *Food Quality Protection Act (FQPA) Considerations*

There was no evidence of increased qualitative or quantitative susceptibility of the offspring in the developmental, reproduction, or developmental neurotoxicity studies. Although increased quantitative susceptibility of the offspring was observed in the comparative ChE study, the degree of concern is low because the effects are well characterized and there are clear NOAELs and LOAELs for both neonatal and adult animals. There are no residual uncertainties for pre- and/or postnatal toxicity for the comparative ChE study because the endpoint of concern is the one used for the acute dietary exposure risk assessment, and a more protective endpoint (based on long-term exposure) is used for chronic dietary exposure risk assessment.

In addition to the hazard data, the coumaphos risk assessment team evaluated the quality of the exposure data and found no residual uncertainties. The acute dietary exposure assessment is based on 2002 PDP monitoring data for beef, 2004 PDP monitoring data for milk, and field trial data for honey and assumes 100% crop treated. The chronic assessment is based on the latest PDP monitoring data for beef and milk, as well as average field trial data for honey; this analysis also assumes 100% crop treated. For water, estimates from conservative Tier 1 screening models were used. By using these conservative assessments, acute and chronic exposures/risks to infants and children will not be underestimated. There are currently no registered or proposed residential uses of coumaphos. Based on the exposure and hazard data, the coumaphos risk assessment team concluded that the FQPA safety factor can be removed (*i.e.*, reduced to 1X).

#### *Residue Chemistry*

Since there are currently no registered or proposed uses of coumaphos on plants, no plant metabolism data are required. The nature of the residue in livestock has been established, based on an adequate cow metabolism study reflecting dermal dosing. In livestock, the residues of concern (ROC) for risk assessment and for tolerance expression are coumaphos and its oxygen analog (coumaphoxon, also referred to as coumaphos-PO). The existing animal data are adequate for purposes of the proposed use on beehives. In honeybee products (honey and honeycomb), the ROC are coumaphos and its oxygen analog.

The available honeybee field trials are adequate, and support the proposed use of coumaphos-impregnated strips (containing 10% ai) in beehives for up to 45 days during honey flow. The number and distribution of the field trials are adequate, and a sufficient number of samples were collected at the appropriate intervals. The field trials are supported by the available storage

stability data, and residues of coumaphos and coumaphos-PO in honey and beeswax were determined using adequate LC/MS/MS methods.

The honey processing data are adequate, and indicate that the processing of raw honey by heating and filtration will reduce coumaphos residues in honey by 0.5x. Coumaphos residues were shown to partition largely into beeswax, which had an average processing factor of approximately 25x.

Adequate LC/MS/MS methods are available for enforcing tolerances and collecting data on residues of coumaphos and coumaphos-PO in honey and beeswax (Bayer Methods #75043 and #75044 for honey and beeswax, respectively).

#### *Dietary Exposure Assessment*

Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The tier 1 GENEEC and SCI-GROW screening models were used to estimate surface water and groundwater concentrations of coumaphos and its oxygen analog, coumaphoxon. The acute assessment incorporated 2002 PDP monitoring data for beef, 2004 PDP monitoring data for milk, and field trial data for honey; this analysis assumes 100% crop treated. Total coumaphos (coumaphos + coumaphoxon) acute estimated environmental concentrations in drinking water derived from surface water sources are not likely to exceed 1.86 ppb. The chronic assessment incorporated the latest PDP monitoring data for beef and milk, as well as average field trial data for honey; this analysis also assumes 100% crop treated. Total coumaphos (coumaphos + coumaphoxon) chronic estimated environmental concentrations in drinking water derived from surface water sources are not likely to exceed 0.41 ppb.

Based on these assumptions, acute dietary risk estimates at the 99.9<sup>th</sup> percentile of exposure are less than or equal to 38% of the acute population-adjusted dose (aPAD) for all population subgroups. Chronic dietary risk estimates are less than or equal to 13% of the chronic population-adjusted dose (cPAD) for all population subgroups. Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute and chronic dietary risk estimates are below HED's level of concern.

#### *Residential Risk*

There are currently no registered or proposed uses of coumaphos in or around residences; therefore, risk assessments for residential (non-occupational) exposure are not warranted at this time.

#### *Aggregate Risk*

The acute and long-term aggregate assessment for coumaphos exposure includes only food and water exposures. Short- and intermediate-term aggregate assessments are not required since none of the currently registered or proposed uses result in residential exposure. Because coumaphos has been classified as a "not likely human carcinogen", a cancer aggregate risk assessment is not required. Estimates of acute and long-term aggregate risks associated with the registered and proposed uses of coumaphos do not exceed HED's level of concern for the

general U.S. population or any population subgroup.

#### *Occupational Risk*

The proposed new use pattern does not indicate significant potential for applicator or post-application dermal or inhalation exposure. The CheckMite+ Bee Hive Pest Control Strips come prepackaged and do not involve any mixing or loading of active ingredient. Occupational exposure resulting from use of these strips is highly improbable, as the only potential times for worker contact are during application, when the beehive keeper removes the strips from the containers and places them in the hives, and during removal and disposal of the strips six weeks later. As indicated previously, coumaphos is not a dermal irritant or a sensitizer. However, in an effort to mitigate any potential for dermal exposure, the proposed label requires the use of chemical resistant gloves by applicators. After six weeks, at the time of disposal, residues have significantly decreased, so post-application exposure is minimal. Since most beehives are located outdoors, there is negligible potential for inhalation exposure, at any time, to the applicator or during post-application activities. Therefore, while short- and intermediate dermal and inhalation endpoints for coumaphos have previously been identified, risk assessments for occupational exposure are not required for this proposed new use.

#### *Environmental Justice Considerations*

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oeпа/guidance/justice/eo12898.pdf>).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Surveys of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

#### *Review of Human Research*

This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

*Recommendations*

Based on the results of our assessment, HED recommends the establishment of the following permanent tolerances for combined residues of coumaphos and coumaphos-PO:

Honey .....	0.15 ppm
Honeycomb .....	45 ppm

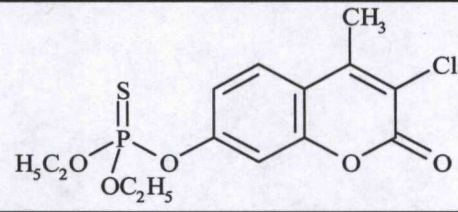
*Additional Data Needs*

None

## 2.0 Ingredient Profile

Coumaphos is an organophosphate insecticide/acaricide currently used for the control of mites and insects in or on livestock. The chemical structure and nomenclature of coumaphos are presented in Table 2.1, and the physicochemical properties of the technical grade coumaphos are presented in Table 2.2. The proposed directions for the new use of coumaphos in beehives are summarized in Table 2.3. The proposed use is similar to currently allowed Section 18 emergency uses, except that the proposed use would allow treatment during honey flow (the period of honey accumulation before harvest). The current Section 18 uses require a 14-day withdrawal period between treatment and the beginning of honey collection.

**Table 2.1. Coumaphos Nomenclature.**

Chemical Structure	
Common Name	Coumaphos
Molecular Formula	C <sub>14</sub> H <sub>16</sub> ClO <sub>5</sub> PS
Molecular Weight	362.78
IUPAC Name	<i>O</i> -3-chloro-4-methyl-2-oxo-2 <i>H</i> -chromen-7-yl <i>O,O</i> -diethyl phosphorothioate
CAS Name	<i>O</i> -(3-chloro-4-methyl-2-oxo-2 <i>H</i> -1-benzopyran-7-yl) <i>O,O</i> -diethyl phosphorothioate
CAS Registry Number	56-72-4
End-use Product (EP)	CheckMite+ Beehive Pest Control Strips (10% ai), EPA Registration #11556-???*
Chemical Class	Organophosphate

\* Not yet registered.

**Table 2.2. Physicochemical Properties of Technical Grade Coumaphos.**

Parameter	Value	Reference
Melting Point/Range	90-95°C	DP #207352, Chris Olinger, 12/12/1994
pH	Not available	
Specific Gravity	1.47	Occupational Health Services MSDS for Coumaphos, 2/12/1991
Water Solubility (20°C)	2.0 mg/100 mL	DP #207352, Chris Olinger, 12/12/1994
Solvent Solubility (g/100 mL at 20°C)	Acetone	
	Diethyl phthalate	
	Ethanol	
	Xylene	
	Octanol	
	Mineral spirits	
	Hexane	
Vapor Pressure (20°C)	1 x 10 <sup>-7</sup> mm Hg	DP #207352, Chris Olinger, 12/12/1994
Dissociation Constant (pK <sub>a</sub> )	Not required	
Octanol/Water Partition Coefficient (Log[K <sub>ow</sub> ])	Not available	
UV/Visible Absorption Spectrum	Not available	

**Table 2.3. Summary of Proposed Directions for the Use of Coumaphos in Beehives.**

Application Timing, Type, and Equipment <sup>1</sup>	Formulation [EPA Reg. #]	Application Rate	Max. # of Applications per Season	Max. Seasonal Application Rate	PHI (Days)
For Control of Varroa Mites					
At anytime during the year, hang strips between combs near center of the brood chamber for 6 weeks.	10% strips [11556-???	1 strip per 5 combs in brood chamber <sup>2</sup>	2	4 strips per hive.	0
For Control of Small Hive Beetles					
At anytime during the year, attach strip to 4x4 inch corrugated plastic or cardboard and place, strip-side down, in center of bottom board. Leave strip in place for 6 weeks.	10% strips [11556-???	1 strip/hive	4	4 strips per hive.	0

1. Do not leave strips in hive for more than 45 days.

2. As a brood chamber typically has 9-10 combs, this would be a rate of 2 strips per hive.

### 3.0 Hazard Characterization/Assessment

#### 3.1 Hazard and Dose-Response Characterization

The mammalian toxicology database for coumaphos is complete. Acute toxicity studies in rats and rabbits; an acute delayed neurotoxicity study in hens; subchronic oral and dermal studies in rats; chronic/carcinogenicity studies in rats, mice, and dogs; developmental toxicity studies in rats and rabbits; a two-generation study in rats; mutagenicity studies; and a metabolism study were discussed and considered in the Reregistration Eligibility Decision (RED) for coumaphos (<http://www.epa.gov/oppsrrd1/REDs/0018.pdf>). Acute and subchronic neurotoxicity studies in rats were received subsequent to the RED and were considered in the Reregistration Eligibility Decision Addendum and FQPA Tolerance Reassessment Progress Report (TRED) for coumaphos (<http://www.epa.gov/oppsrrd1/REDs/0018tred.pdf>). Subsequent to the TRED, a developmental neurotoxicity study and a comparative cholinesterase study in rats were received; these studies are discussed below and were considered in the current risk assessment.

The acute toxicity of coumaphos is high via the oral route of exposure (Category I), moderate via the inhalation route (Category II), and slight via the dermal route (Category III). Coumaphos is not a dermal sensitizer or a dermal irritant.

Coumaphos, an organophosphate insecticide, primarily affects the nervous system through cholinesterase (ChE) inhibition. Females are consistently more sensitive to the cholinergic effects than males. In the acute oral toxicity studies, female rats are approximately 17 times more sensitive to the toxic and lethal effects of coumaphos compared to male rats. In a single dose oral study, female rats had ChE inhibition and cholinergic symptoms at much lower doses than male rats. In a short-term (5 days) dermal toxicity study, brain ChE inhibition was the most sensitive indication of the toxic effects of coumaphos dermal treatment. In subchronic and chronic studies in rats, the magnitude of ChE inhibition in red blood cell and plasma and brain was also more pronounced in females, compared to males. Coumaphos does not cause delayed neuropathy. In chronic studies, systemic effects other than cholinergic toxicity include decreases

in body weight gain.

There was no evidence of malformations or decreases in the number of pups and/or litter or surviving offspring in any of the developmental toxicity or reproduction studies. In developmental toxicity studies in rats and rabbits, no developmental toxicity was observed, while clinical signs of ChE toxicity were seen in the maternal animals. In a two-generation reproduction study, ChE inhibition was noted in both parents and offspring, with parents more susceptible. Reproductive toxicity was not observed in this study.

In a developmental neurotoxicity study (MRID 45912101), coumaphos was administered to 30 parent female Wistar rats/dose in the diet at concentrations of 0, 1, 5, or 30 ppm from gestation day 0 through postnatal day 21. The average daily intake of coumaphos was 0, 0.09, 0.47, and 2.77 mg/kg/day during gestation and 0, 0.22, 1.06, and 7.40 mg/kg/day during lactation, for the 0, 1, 5, and 30 ppm groups, respectively. In the dams, the maternal LOAEL was based on 21% and 78% inhibition of plasma and erythrocyte ChE activities, respectively, at the mid dose (0.47 mg/kg/day). Higher inhibition of plasma and erythrocyte ChE activities (68% and 85%, respectively), as well as brain ChE inhibition (36%), was observed at the high dose. In offspring, changes in brain morphometry in PND 21 males, as well as inhibition of plasma, erythrocyte, and brain ChE activities, were noted only at the high dose. Since no effects, including ChE inhibition, were seen in the offspring at the mid dose, where ChE activities were depressed in dams at this same dose, the developmental neurotoxicity study shows that there is no increased susceptibility of the young. Consistent with the other mammalian toxicity studies, female pups were more sensitive to cholinergic effects than males; at the high dose, female plasma, erythrocyte, and brain ChE activities were inhibited 27%, 33%, and 8%, respectively, but only plasma ChE activity was significantly inhibited (30%) at this dose in males.

The relative sensitivities to ChE inhibition at peak inhibition by coumaphos were measured in neonatal and young adult Wistar rats (MRID 46258301). In these studies, coumaphos was administered in a single gavage dose of 0, 0.25, 0.50, or 1.0 mg/kg/day to neonatal (postnatal day 11) rats and of 0, 1.0, 2.0 or 4.0 mg/kg/day to young adult (postnatal day 58-63) rats. Peak ChE inhibition was measured 8 or 4 hours following dosing to young adult or neonatal rats, respectively. In young adults, the NOAEL/LOAEL was 1.0/2.0 mg/kg, based on plasma (male/females=33%/38%) and erythrocyte (males/females=34%/30%) ChE inhibition. Brain ChE activities were not inhibited at any dose level in males or females. In neonates, the NOAEL/LOAEL was 0.25/0.5 mg/kg based on plasma (males/females 19%/22%), erythrocyte (males /females 20%/19%), and brain (8%/7%) ChE inhibition. The study shows that coumaphos treatment of PND 11 male and female pups by a single gavage dose results in ChE inhibition at a lower dose than similar treatment of PND 58-63 male and female young adults. In addition, brain ChE was inhibited at the same LOAEL as plasma and erythrocyte ChE in male and female neonatal pups, whereas young adults showed no brain ChE inhibition at any dose level in males or females. Therefore, this comparative ChE study does demonstrate increased quantitative susceptibility of the offspring.

Coumaphos is not carcinogenic and is classified as a Group E chemical, indicating that it is "Not Likely" to be carcinogenic in humans via relevant routes of exposure. This classification is

based on adequate studies in two animal species. No evidence of mutagenicity was seen in any study.

Following oral administration, coumaphos is rapidly broken down into nontoxic metabolites and eliminated in urine and feces with no evidence of bioaccumulation. The plasma half-life ranges from approximately 3 to 5 hours. Tissue residues of coumaphos are highest in fat, kidney, liver and muscle. Approximately 63 - 83% of administered dose is excreted in the urine within 24 hours and 76-96% is excreted within 7 days. Dermal absorption is estimated to be 100%. This estimate is based on the observation that erythrocyte ChE inhibition is observed in both oral and dermal rat studies at similar dose levels. Inhalation absorption is also assumed to be 100%.

### **3.2 FQPA Considerations**

As of December 2006, the mammalian toxicology database for coumaphos is complete for FQPA considerations, including an acceptable two-generation reproduction study in rats; acceptable prenatal developmental toxicity studies in rats and rabbits; acceptable acute, subchronic, and developmental neurotoxicity studies in rats, and an acceptable comparative ChE assay in rats. There was no evidence of increased qualitative or quantitative susceptibility of the offspring in the developmental, reproduction, or developmental neurotoxicity studies. Increased quantitative susceptibility of the offspring was observed in the comparative ChE study in that ChE inhibition was seen at a lower dose in neonatal rats, compared to young adult rats. The degree of concern for this comparative ChE study is low because the effects are well characterized and there are clear NOAELs and LOAELs for both neonatal and adult animals. Furthermore, there are no residual uncertainties for pre- and/or postnatal toxicity for the comparative ChE study because the endpoint of concern is the one used for the acute dietary exposure risk assessment and a more protective endpoint (based on long-term exposure) is used for chronic dietary exposure risk assessment.

In addition to the hazard data, the coumaphos risk assessment team evaluated the quality of the exposure data and found no residual uncertainties. The acute dietary exposure assessment is based on 2002 PDP monitoring data for beef, 2004 PDP monitoring data for milk, and field trial data for honey and assumes 100% crop treated. The chronic assessment is based on the latest PDP monitoring data for beef and milk, as well as average field trial data for honey; this analysis also assumes 100% crop treated. For water, estimates from conservative Tier 1 screening models were used. By using these conservative assessments, acute and chronic exposures/risks to infants and children will not be underestimated. There are currently no registered or proposed residential uses of coumaphos. Based on the exposure and hazard data, the coumaphos risk assessment team concluded that the FQPA safety factor can be reduced to 1X.

### **3.3 Hazard Identification and Toxicity Endpoint Selection**

#### **3.3.1 Acute Reference Dose (aRfD) - Females age 13-49**

A separate acute dietary endpoint for females age 13-49 years was not selected because coumaphos does not induce any effects attributable to a single dose, including developmental effects, that would affect this population subgroup.

### **3.3.2 Acute Reference Dose (aRfD) - General Population**

**Study Selected:** Comparative cholinesterase (ChE) study in rats

**MRID Number:** 46258301

**Dose and Endpoint for Establishing aRfD:** 0.25 mg/kg (NOAEL), based on plasma (19%/22%; M/F), RBC (20%/19%; M/F), and brain (8%/7%; M/F) ChE inhibition in PND 11 males and females observed at 0.5 mg/kg (LOAEL)

**Uncertainty Factor(s):** 100X (10X for interspecies variability, 10X for intraspecies variability)

**Comments about Study/Endpoint/Uncertainty Factor:**

The acute dietary endpoint for the general population is based on plasma, erythrocyte and brain ChE inhibition (measured at time of peak inhibition) in PND 11 rats following a single oral dose in the comparative ChE study. This endpoint is considered appropriate for the general population because the effects were observed following a single dose, and the route of administration (oral) is appropriate for dietary considerations. Previously, the acute dietary endpoint was based on plasma and erythrocyte ChE inhibition observed in rats at a LOAEL of 2 mg/kg (no NOAEL was observed) in an acute neurotoxicity study. The newly selected endpoint is protective of this effect, as well as all others seen in the mammalian toxicology database attributable to a single dose.

### **3.3.3 Chronic Reference Dose (cRfD)**

**Study Selected:** Chronic toxicity study in dogs

**MRID Number:** 43055301

**Dose and Endpoint for Establishing cRfD:** 0.025 mg/kg (NOAEL), based on plasma and RBC ChE inhibition in males and females observed at 0.775/0.705 mg/kg/day (LOAEL; M/F)

**Uncertainty Factor(s):** 100X (10X for interspecies variability, 10X for intraspecies variability)

**Comments about Study/Endpoint/Uncertainty Factor:**

The chronic dietary endpoint is based on plasma and RBC ChE inhibition in males and females in the chronic toxicity study in dogs. This endpoint is considered appropriate for chronic dietary exposure due to the oral route of administration and the chronic duration of exposure. The study and endpoint were selected because they are protective of effects observed in all the other available studies, including offspring effects seen in the recently submitted developmental neurotoxicity study.

### **3.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)**

There are currently no registered or proposed uses of coumaphos in or around residences; therefore, incidental oral exposure is not expected and an incidental oral exposure assessment is not warranted at this time.

### 3.3.5 Dermal Absorption

Previously, the HED HIARC determined that in the absence of dermal absorption data and considering the observation that erythrocyte ChE inhibition is observed in both oral gavage and dermal rat studies at similar dose levels, the default of 100% absorption should be used. However, note that the proposed use on beehives is not residential and is unlikely to result in occupational dermal exposure; therefore, a dermal exposure assessment is not required for this risk assessment.

### 3.3.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

To assess **short-term dermal** exposure, the HED HIARC previously determined that a dermal NOAEL of 5.0 mg/kg/day should be used, based on brain ChE inhibition in female rats at 10 mg/kg/day from a 5-day dermal toxicity study (MRID 44749401). To assess **intermediate-term dermal** exposure, the HED HIARC previously determined that a dermal NOAEL of 0.5 mg/kg/day should be used, based on RBC ChE inhibition in female rats at 1.1 mg/kg/day from a 21-day dermal toxicity study (MRID 42084901). A dose and endpoint have not been selected to assess **long-term dermal** exposure because the use pattern and exposure scenarios for the registered and proposed uses do not indicate a need for long-term dermal risk assessment.

Note that because the proposed use is not residential and is unlikely to result in occupational dermal exposure, a dermal exposure assessment is not required for this risk assessment.

### 3.3.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

To assess **short-term inhalation** exposure, the HED HIARC previously determined that an oral LOAEL of 2.0 mg/kg should be used (a NOAEL was not determined), based on plasma and RBC ChE inhibition in male and female rats from an acute neurotoxicity study (MRID 44544801). To assess **intermediate-term inhalation** exposure, the HED HIARC previously determined that an oral LOAEL of 0.2 mg/kg/day should be used (a NOAEL was not determined), based on RBC ChE inhibition in rats from a subchronic feeding study in rats (MRID 00126527). A dose and endpoint have not been selected to assess **long-term inhalation** exposure because the use pattern and exposure scenarios for the registered and proposed uses do not indicate a need for long-term inhalation risk assessment.

Note that because the proposed use is not residential and is unlikely to result in occupational inhalation exposure, an inhalation exposure assessment is not required for this risk assessment.

### 3.3.8 Level of Concern for Margin of Exposure

Residential and occupational exposure assessments are not required for the risk assessment of the proposed use of coumaphos on beehives. See sections 6.0 and 9.0 for more details.

### 3.3.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. At this time, an aggregated exposure risk assessment across these routes of exposure is not required since there are no registered or proposed residential uses for coumaphos. The aggregate assessment, in this case, consists of just the dietary sources of exposure (*i.e.*, food and water).

### 3.3.10 Classification of Carcinogenic Potential

Coumaphos is classified as a Group E chemical, indicating that it is "Not Likely" to be carcinogenic in humans via relevant routes of exposure. This classification is based on adequate studies in two animal species. No evidence of mutagenicity was seen in any study.

### 3.3.11 Summary of Toxicological Doses and Endpoints for Coumaphos for Use in Human Risk Assessments

Table 3.3.11a. Toxicological Doses and Endpoints for Coumaphos for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure/Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 0.25 mg/kg	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	Acute RfD = 0.0025 mg/kg  aPAD = 0.0025 mg/kg/day	Comparative cholinesterase study in rats LOAEL = 0.5 mg/kg based on plasma (19%/22%; M/F), RBC (20%/19%; M/F), and brain (8%/7%; M/F) ChE inhibition in PND 11 males and females
Chronic Dietary (All Populations)	NOAEL = 0.025 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	Chronic RfD = 0.00025 mg/kg/day  cPAD = 0.0003 mg/kg/day	Chronic toxicity study in dogs LOAEL = 0.775/0.705 mg/kg/day (M/F) based on plasma and RBC ChE inhibition in males and females
Incidental Oral (All Durations)	The proposed use is not residential, so incidental oral exposure is not expected.			
Dermal (All Durations)	The proposed use is not residential, so dermal exposure due to residential use is not expected.			
Inhalation (All Durations)	The proposed use is not residential, so inhalation exposure due to residential use is not expected.			
Cancer	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). UF<sub>DB</sub> = to account for the absence of key data (*i.e.*, lack of a developmental immunotoxicity study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

<b>Table 3.3.11b. Summary of Toxicological Doses and Endpoints for Coumaphos for Use in Occupational Human Health Risk Assessments.</b>				
<b>Exposure/Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty Factors</b>	<b>Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Dermal (All Durations)	The proposed use is unlikely to result in occupational dermal exposure, so a dermal exposure assessment is not required for this risk assessment.			
Inhalation (All Durations)	The proposed use is unlikely to result in occupational inhalation exposure, so an inhalation exposure assessment is not required for this risk assessment.			
Cancer	Classification: "Not likely to be Carcinogenic to Humans"			

### **3.4 Endocrine Disruption**

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on coumaphos, there was no estrogen-, androgen-, and/or thyroid-mediated toxicity.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, coumaphos may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

### **4.0 Public Health and Pesticide Epidemiology Data**

No public health or epidemiology data were used in the development of this risk assessment.

### **5.0 Dietary Exposure/Risk Characterization**

- HED Residue Chemistry Summary Document (D334589, W. Drew, 2/29/2007)
- HED Dietary Exposure Memo (D335163, S. Piper, 1/9/2007)
- Reregistration Eligibility Decision (<http://www.epa.gov/oppsrrd1/REDs/0018.pdf>)
- Reregistration Eligibility Decision Addendum and FQPA Tolerance Reassessment Progress Report (TRED) for coumaphos (<http://www.epa.gov/oppsrrd1/REDs/0018tred.pdf>)

### **5.1 Pesticide Metabolism and Environmental Degradation**

### **5.1.1 Metabolism in Primary Crops**

No primary crop metabolism data are required, as coumaphos is not registered for use on plants.

### **5.1.2 Metabolism in Rotational Crops**

No rotational crop metabolism data are required, as coumaphos is not registered for use on plants.

### **5.1.3 Metabolism in Livestock**

The nature of the residue in livestock has been established, based on an adequate cow metabolism study reflecting dermal dosing. In livestock, the residues of concern (ROC) for risk assessment and for tolerance expression are coumaphos and its oxygen analog (coumaphoxon, also referred to as coumaphos-PO).

The existing animal data are adequate for purposes of the proposed use on beehives. In honeybee products (honey and honeycomb), the ROC are coumaphos and its oxygen analog.

### **5.1.4 Analytical Methodology**

Adequate LC/MS/MS methods are available to collect residue data and enforce tolerances for coumaphos and its oxygen analog (coumaphos-PO) in honey (Bayer Method 75043) and honeycomb (Bayer Method 75044). The limits of quantitation (LOQs) for both coumaphos and coumaphos-PO are 0.010 ppm in honey and 0.50 ppm in honeycomb (beeswax). The limits of detection (LODs) were not reported.

For Bayer Method 75043, residues in honey are extracted by dissolving the sample in 10% methanol in water. Residues are then cleaned up using a C<sub>2</sub> solid phase extraction (SPE) cartridge eluted with 70% ACN in water, and the residues in the resulting eluate were analyzed by LC/MS/MS. For Bayer Method 75044, residues in beeswax are extracted by dissolving the sample in isopropanol at 65°C for 15-20 minutes, and then diluting the extract with 0.1N NaOH at 65°C. Residues in the extract are then purified using a ChemElut column. After loading, the column is rinsed with 5N formic acid, residues are eluted with ethyl ether, and then concentrated. Residues are then re-dissolved in 70% ACN in water, filtered, and analyzed via LC/MS/MS.

Both methods used the same parameters for the LC/MS/MS analysis. Residues are separated using a reverse-phase ODS-2 column at 30°C, with an isocratic solvent gradient of ACN/water (4:1), each containing 0.1% acetic acid. The retention times for coumaphos and coumaphos-PO are approximately 4.6 and 2.9 minutes, respectively. Residues are quantified by MS/MS using the m/z 363 to 227 transition for coumaphos and the m/z 347 to 291 transition for coumaphos-PO. The validated LOQs for both compounds are 0.010 ppm in honey and 0.50 ppm in beeswax; method LODs were not reported.

The methods were subjected to independent laboratory validation (ILV) studies. For Method 75043, the overall average recovery of coumaphos from honey was 94% (with standard deviation of 2%), and the overall average recovery of coumaphos-PO was 93% (std. dev. 6%). The calibration curve correlation coefficients for coumaphos ranged from 0.9973 to 0.9999, while those for coumaphos-PO ranged from 0.9979 to 0.9999. For Method 75044, the overall average recovery of coumaphos from honeycomb was 77% (std. dev. 3%), and the overall average recovery of coumaphos-PO was 80% (std. dev. 7%). The calibration curve correlation coefficient for coumaphos was 0.9971, while that for coumaphos-PO was 0.9984.

These methods were also validated in conjunction with the analysis of beehive field trial samples, using control samples of honey fortified with each analyte at 0.010 and 0.100 ppm and control samples of beeswax fortified with each analyte at 0.50-5.00 ppm.

Based on communications with FDA laboratories, the existing FDA multiresidue methods can be used to enforce coumaphos and coumaphos oxon tolerances in honey using the Luke or 'modified' Luke procedures. However, it is uncertain whether residues of the parent or oxon in beeswax can be determined by the multiresidue Luke method since the 'wax' would probably present interference problems.

#### 5.1.5 Environmental Degradation

Coumaphos is persistent in the environment, with the exception that aqueous photolysis is rapid (half-life 33 hours). The half-life is much greater than 30 days for hydrolysis; much greater than a year for aerobic soil metabolism; and ca. 118 to 185 days for field dissipation. Coumaphos also appears to be immobile, with  $K_d$  values ranging from 61 to 298 for parent and from 91 to 161 for the degradate chlorferon. Coumaphos accounted for 0.4% of leachate from a sandy loam column and less than 2% of leachate from columns of sand, silt loam, and silty clay loam.

#### 5.1.6 Pesticide Metabolites and Degradates of Concern

**Table 5.1.6. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.**

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Not Applicable <sup>1</sup>	Not Applicable <sup>1</sup>
	Rotational Crop	Not Applicable <sup>1</sup>	Not Applicable <sup>1</sup>
Livestock	Ruminant	Parent and Coumaphoxon	Parent and Coumaphoxon
	Poultry	Not Applicable <sup>2</sup>	Not Applicable <sup>2</sup>
Drinking Water		Parent and Coumaphoxon	Parent and Coumaphoxon

<sup>1</sup> There are currently no registered or proposed uses of coumaphos on plants.

<sup>2</sup> There are currently no registered or proposed uses of coumaphos on poultry.

#### 5.1.7 Drinking Water Residue Profile

The GENEEC and SCI-GROW screening models were used to estimate surface water and groundwater concentrations of coumaphos and its oxygen analog, coumaphoxon. This degradate is considered in the drinking water assessment, as it was in the assessment for consumption of food (honey and livestock commodities). The acute and chronic surface values were incorporated directly into these dietary assessments under the DEEM-FCID food categories “water, all sources” and “water, indirect, all sources.” The model and its description are available at the EPA internet site: <http://www.epa.gov/oppefed1/models/water/>.

Tier I GENEEC screening model, representing a worst-case runoff scenario for pesticides in surface water, was used to estimate the upper-bound concentrations in surface water. Total coumaphos (coumaphos + coumaphoxon) acute and chronic estimated environmental concentrations in drinking water derived from surface water sources are not likely to exceed 1.86 ppb and 0.41 ppb, respectively.

A Tier I screening model, SCI-GROW, was used to estimate total coumaphos concentrations in ground water. This is an empirical model based on field data from prospective ground water studies. Estimated environmental concentration of total coumaphos, representing acute and chronic exposures to ground water, is 0.17 ppb.

The recommended application rate for coumaphos spent solution from dip vat operations on non-agricultural land is 10,000 liters (L) of coumaphos spent solution containing 10 ppb spread over a one-acre field. A conversion efficiency of coumaphos to coumaphoxon of 10.2% was derived from available (supplemental) data on photodegradation in water. This conversion efficiency was used to estimate a coumaphoxon application rate of 0.02 lbs ai/A.

Total coumaphos (coumaphos + coumaphoxon) acute and chronic estimated environmental concentrations in drinking water were derived from surface water sources. HED believes the environmental concentrations (EECs) are still conservative estimates because most of the coumaphos spent solution resulting from the dip use on livestock is collected and transported to concrete-lined evaporation pits, thereby negating any potential for groundwater contamination.

<b>Table 5.1.7. Summary of Estimated Surface Water and Groundwater Concentrations for Coumaphos and Coumaphoxon.</b>		
	<b>Surface Water Conc., ppb <sup>a</sup></b>	<b>Groundwater Conc., ppb <sup>b</sup></b>
Acute	1.86	0.17
Chronic (non-cancer)	0.41	0.17
Chronic (cancer)	N/A	N/A
<sup>a</sup> From the Tier 1 GENEEC model.		
<sup>b</sup> From the Tier 1 SCI-GROW model.		

### **5.1.8 Food Residue Profile**

The available honeybee field trials are adequate, and support the proposed use of coumaphos-impregnated strips (containing 10% ai) in beehives for up to 45 days during honey flow. The

number and distribution of the field trials are adequate, and a sufficient number of samples were collected at the appropriate intervals. The field trials are supported by the available storage stability data, and residues of coumaphos and coumaphos-PO in honey and beeswax were determined using adequate LC/MS/MS methods.

The honey processing data are adequate, and indicate that the processing of raw honey by heating and filtration will reduce coumaphos residues in honey by 0.5x. Coumaphos residues were shown to partition largely into beeswax, which had an average processing factor of approximately 25x.

#### **5.1.9 International Residue Limits**

There are Canadian MRLs set at 0.5 mg/kg, calculated on the fat content, for coumaphos (defined as coumaphos, *per se*) in meat, meat byproducts, and fat of cattle, goats, horses, hogs, poultry, and sheep. As of December 2006, there are currently no Mexican or Codex MRLs for coumaphos.

### **5.2 Dietary Exposure and Risk**

HED Dietary Exposure Memo (D335163, S. Piper, 1/9/2007)

Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Cancer dietary exposure and risk assessments are not required since coumaphos is classified as "Not likely to be Carcinogenic to Humans". The dietary exposure and risk assessments for coumaphos include the following: (1) Section 3 requests for coumaphos in honey; (2) a new acute toxicological endpoint; (3) and the latest monitoring data for beef and milk. Table 5.2 presents a summary of the acute and chronic dietary exposure and risk estimates for coumaphos.

#### **5.2.1 Acute Dietary Exposure/Risk**

A partially refined acute dietary exposure assessment was conducted to estimate the dietary exposure and risk associated with the registration of coumaphos. The acute dietary exposure assessment incorporated 2002 PDP monitoring data for beef and 2004 PDP monitoring data for milk. Field trial data were used for honey and support the proposed use pattern. The dietary exposure assessment assumes 100% crop treated for the acute analysis.

The GENEEC and SCI-GROW screening models were used to estimate surface water and groundwater concentrations of coumaphos and its oxygen analog, coumaphoxon. Tier 1 GENEEC screening model, representing a worst-case runoff scenario for pesticides in surface water, was used to estimate the upper-bound concentrations in surface water. Total coumaphos (coumaphos + coumaphoxon) acute estimated environmental concentrations in drinking water derived from surface water sources are not likely to exceed 1.86 ppb.

The acute dietary risk estimates are below HED's level of concern (<100 % aPAD) for the U.S. population and all population subgroups. Combined dietary exposure from food and drinking water at the 99.9<sup>th</sup> percentile of exposure is 15% of the aPAD for the U.S. population and 38% of the aPAD for all infants (<1 yr), the most highly exposed population subgroup.

### 5.2.2 Chronic Dietary Exposure/Risk

A partially refined chronic dietary exposure assessment was conducted to estimate the dietary risks associated with the registration of coumaphos. The chronic dietary exposure assessment incorporated the latest PDP monitoring data, average field trial data for honey, and assumed 100% crop treated. Total coumaphos (coumaphos + coumaphoxon) chronic estimated environmental concentrations in drinking water derived from surface water sources are not likely to exceed 0.41 ppb.

The chronic dietary risk estimates are below HED's level of concern (< 100% of the cPAD) for the U.S. population and all population subgroups. Combined dietary exposure from food and drinking water is 6% of cPAD for the U.S. population and 13% of the cPAD for all infants (<1 yr), the most highly exposed population subgroup.

**Table 5.2. Summary of the Dietary Exposure and Risk Estimates for Coumaphos.**

Population Subgroup	Acute Dietary (99.9 Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.000370	15	0.000015	5.9	N/A	N/A
<b>All Infants (&lt; 1 year)</b>	<b>0.000945</b>	<b>38</b>	<b>0.000032</b>	<b>13</b>		
Children 1-2 years	0.000399	16	0.000027	11		
Children 3-5 years	0.000383	15	0.000025	10		
Children 6-12 years	0.000239	9.6	0.000018	7.1		
Youth 13-19 years	0.000252	10	0.000012	5.0		
Adults 20-49 years	0.000276	11	0.000013	5.3		
Adults 50+ years	0.000199	8.0	0.000013	5.1		
Females 13-49 years	0.000263	11	0.000012	5.0		

### 5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The acute dietary assessment is based on PDP monitoring data for beef and milk and on field trial data for honey; the acute analysis assumes 100% crop treated. The chronic dietary exposure is based on PDP monitoring data for beef and milk and on average residues from field trials on

honey; the chronic analysis assumes 100% crop treated.

## **6.0 Residential (Non-Occupational) Exposure/Risk Characterization**

There are currently no registered or proposed uses of coumaphos in or around residences; therefore, risk assessments for residential (non-occupational) exposure are not warranted at this time.

## **7.0 Aggregate Risk Assessments and Risk Characterization**

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from dietary and residential sources are added together and compared to quantitative estimates of hazard (*e.g.*, a NOAEL), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Because there are no residential uses for coumaphos at this time, the aggregate assessments include dietary exposures only.

### **7.1 Acute Aggregate Risk**

Rather than using back-calculated drinking water levels of comparison (DWLOCs), estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate acute risk. Therefore, the acute aggregate risk estimates are equivalent to the acute dietary risk estimates provided in Table 5.2. The acute aggregate risks associated with the registered and proposed uses of coumaphos do not exceed HED's level of concern for the general U.S. population or any population subgroup.

### **7.2 Short- and Intermediate-Term Aggregate Risk**

Short- and intermediate-term aggregate assessments are not required since none of the currently registered or proposed uses result in residential exposure.

### **7.3 Long-Term Aggregate Risk**

None of the currently registered or proposed uses result in residential exposure. Estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate chronic risk. Therefore, the long-term aggregate risk estimates are equivalent to the chronic dietary risk estimates provided in Table 5.2. The long-term aggregate risks associated with the registered and proposed uses of coumaphos do not exceed HED's level of concern for the general U.S. population or any population subgroup.

### **7.4 Cancer Risk**

Coumaphos has been classified by HED HIARC as "Not likely to be Carcinogenic to Humans"; a cancer aggregate risk assessment is not required.

## **8.0 Cumulative Risk Characterization/Assessment**

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, the EPA shall consider, among other things, available information concerning the cumulative effects on human health that may result from dietary, residential, or other non-occupational exposure to the pesticide chemical and other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the substances individually. A person exposed to a pesticide at a level that is considered safe may, in fact, experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

The organophosphate pesticides (OPs) were established as the first common mechanism group by EPA in 1999, based on their shared ability to bind to and phosphorylate the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems. Coumaphos is an OP pesticide. In December 2001, the Agency issued the "Preliminary OP Cumulative Risk Assessment", available at [http://www.epa.gov/pesticides/cumulative/pr\\_a\\_op\\_methods.htm](http://www.epa.gov/pesticides/cumulative/pr_a_op_methods.htm). In June 2002, the Agency released its Revised OP CRA, available at <http://www.epa.gov/pesticides/cumulative/rra-op/>, which included the cumulative risk due to the OPs from exposures in food, drinking water, and residential uses. In August 2006, the Agency issued an update to the 2002 Revised OP CRA document, which emphasized changes, modifications, and amendments. With the 2006 update, available at <http://www.epa.gov/pesticides/cumulative/2006-op/index.htm>, the Agency has developed a highly refined and complex cumulative risk assessment for the OPs that represents the state of the science regarding existing hazard and exposure data and the models and approaches used. In accordance with the August 2006 deadline under the FQPA, the Agency concluded that the results of the OP cumulative risk assessment support a reasonable certainty of no harm finding.

In both the 2002 revised OP CRA, as well as the 2006 update, the cumulative dietary risk associated with the use of OP pesticides on food crops was assessed using residue monitoring data collected by the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP) and dietary consumption data collected by USDA's Continuing Survey of Food Intakes by Individuals (CSFII). Both assessments relied primarily on the PDP for residue data; the 2006 update added PDP data collected in 2002-2004 to the 1994-2001 data used in the 2002 Revised Assessment. The PDP has been collecting pesticide residue data since 1991, primarily for purposes of estimating dietary exposure. The program focuses on high-consumption foods for children and reflects foods typically available throughout the year. A complete description of the PDP and all data through 2004 are available online (<http://www.ams.usda.gov/science/pdp>). No PDP data on honey currently exist that could have been used in a cumulative assessment. OP

residues in honey were not included in the PDP database, in part because honey is a low-consumption food. A quantitative estimate of honey consumption over a single day was obtained for the general U.S. population and subpopulations using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998 (personal correspondence, D. Hrdy, 2/1/2007). Consumption estimates at the 99.9<sup>th</sup> percentile of exposure range from 21 grams of honey/day in all infants (<1 yr) to 96 grams/day in adults 50+ years, the population subgroup who reported the greatest amount of honey consumed. Estimates of honey consumption for all other subpopulations, including children 1-2, 3-5, and 6-12 years; youth 13-19 years; females 13-49 years; and adults 20-49 years are within this range.

Although PDP data on coumaphos data in honey is not available, monitoring for coumaphos in honey is conducted under the Food and Drug Administration's (FDA's) Center for Food Safety and Applied Nutrition (CFSAN) Surveillance Monitoring Program. This monitoring program is designed primarily for enforcement of EPA pesticide tolerances on imported foods and domestic foods shipped in interstate commerce. In this monitoring program, domestic samples are generally collected close to the point of production in the distribution system. Import samples are collected at the point of entry into US commerce. The emphasis in sample collection is on the agricultural commodity, which is analyzed as the unwashed, whole (unpeeled), raw commodity. Processed foods are also included in the program. A description of the program and residue data for recent years can be found online (<http://vm.cfsan.fda.gov/~lrd/pestadd.html>). Because the emphasis of this program is not on dietary exposure, it was used in the 2006 cumulative assessment mostly as a semi-quantitative check on the potential for residues and as support for data from other sources. Data are available from 1996-2003. Although the Agency has granted emergency exemptions, starting in 1999, such that the coumaphos strips assessed in this document have been and continue to be used on beehives in 40-46 states (<http://www.epa.gov/opprd001/section18>), the FDA has detected coumaphos in honey only once, in 2003, at levels lower than the level of quantification. Thus, FDA data indicates that there is a low expectation of meaningful coumaphos residues in honey.

EPA does not believe that inclusion of anticipated coumaphos residues in honey in the OP CRA will significantly modify the calculated risk. This conclusion is based on three factors. First, honey is a low consumption food, and, thus, even if honey contained quantifiable levels of OPs, it would be unlikely to significantly alter the OP CRA. Second, available monitoring data indicates that, despite widespread use of coumaphos, residues of coumaphos in honey as consumed are exceedingly low, if present at all. Finally, a prior risk assessment for coumaphos indicated that aggregate risk from coumaphos was essentially unchanged when honey containing levels of coumaphos residues found in field trials was added to the coumaphos risk assessment. (65 FR 49927, 49934-49935, August 16, 2000). In the current assessment, no discernible difference in exposure was observed when coumaphos residues in honey and beeswax were or were not included in an aggregate assessment (personal correspondence, S. Piper, 1/25/2007). If coumaphos exposure from honey is insignificant in comparison to exposure to coumaphos from other uses of the chemical, it necessarily is insignificant in comparison to exposure to the more than 30 other OPs. For these reasons, EPA concludes that the establishment of a coumaphos

honey tolerance will not raise a concern regarding cumulative OP exposure.

## **9.0 Occupational Exposure/Risk Pathway**

**HED Occupational/Residential Exposure Memo, (D263035, M. Collantes, 2/11/2000)**

This risk assessment addresses the proposed permanent new use of coumaphos on beehives. The end use product, CheckMite+ Bee Hive Pest Control Strips, consists of plastic strips that are impregnated with 10% liquid solution of the active ingredient, coumaphos. These strips come prepackaged and do not involve any mixing or loading of active ingredient. As previously mentioned, the proposed label would allow for use of up to two strips hung in the hive's brood chamber for control of varroa mites, and the concurrent use of another 10% strip attached to the bottom board for control of small hive beetles. The strips could remain in the hive for up to 45 days.

This specific use pattern does not indicate significant potential for applicator or post-application dermal or inhalation exposure. Occupational exposure resulting from use of these strips is highly improbable, as the only potential times for worker contact are during application, when the beehive keeper removes the strips from the containers and places them in the hives, and during removal and disposal of the strips six weeks later. As indicated previously, coumaphos is not a dermal irritant or a sensitizer. However, in an effort to mitigate any potential for dermal exposure, the proposed label requires the use of chemical resistant gloves by applicators. After six weeks, at the time of disposal, residues have significantly decreased, so post-application exposure is minimal. Since most beehives are located outdoors, there is negligible potential for inhalation exposure, at any time, to the applicator or during post-application activities. Therefore, while short- and intermediate dermal and inhalation endpoints for coumaphos have previously been identified, risk assessments for occupational exposure are not required for this proposed new use.

## **10.0 Data Needs and Label Recommendations**

### **10.1 Toxicology**

None

### **10.2 Residue Chemistry**

None

### **10.3 Occupational and Residential Exposure**

None

## References:

- HED Residue Chemistry Summary Document (D334589, W. Drew, 2/28/2007)
- HED Dietary Exposure Memo (D335163, S. Piper, 1/9/2007)
- HED Occupational/Residential Exposure Memo, (D263035, M. Collantes, 2/11/2000)
- Reregistration Eligibility Decision (RED) (<http://www.epa.gov/oppsrrd1/REDs/0018.pdf>)
- Reregistration Eligibility Decision Addendum and FQPA Tolerance Reassessment Progress Report (TRED) (<http://www.epa.gov/oppsrrd1/REDs/0018tred.pdf>)
- Personal correspondence from D. Hrды to K. Schumacher (2/1/2007, 04:09 PM)
- Personal correspondence from S. Piper to K. Schumacher (1/25/2007, 02:38 PM)

## Appendix A: Toxicology Assessment

### A.1 Toxicity Profile

Table A.1 is identical to the acute toxicity profile table included in "The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Coumaphos" (J. Redden, 4/21/1995).

Table A.1 Acute Toxicity Profile - Coumaphos				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
81-1	Acute oral - rat	00110597	LD <sub>50</sub> > 240 mg/kg (♂) LD <sub>50</sub> = 17 mg/kg (♀)	I
81-2	Acute dermal - rat	00110598	LD <sub>50</sub> > 2400 mg/kg (♂+♀)	III
81-3	Acute inhalation - rat	00110601	LC <sub>50</sub> = 1.081 mg/L (♂) LC <sub>50</sub> = 0.341 mg/L (♀)	II
81-4	Acute eye irritation - rabbit	00110599	Mild irritant, resolved by day 7	III
81-5	Acute dermal irritation - rabbit	00110600	Not irritating	IV
81-6	Skin sensitization - rabbit	00110602	Not a sensitizer	N/A